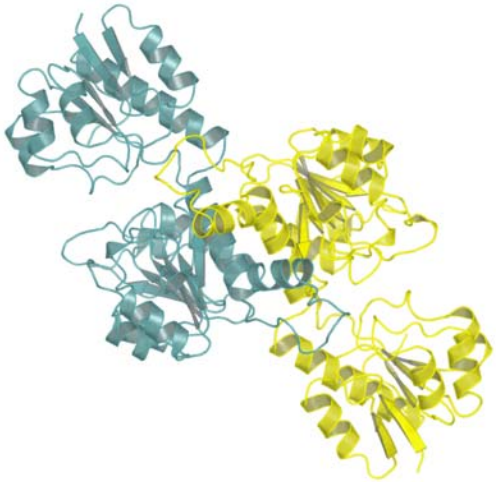
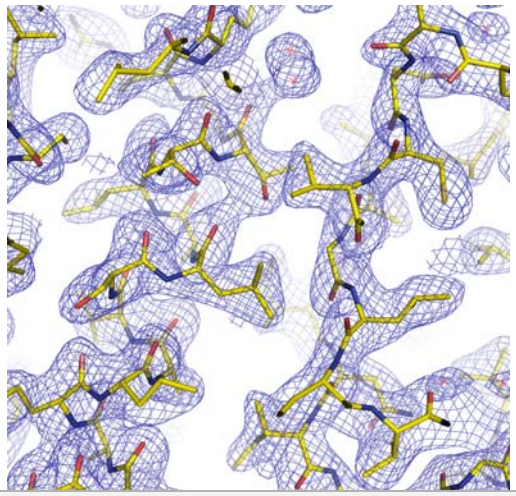
Center for Eukaryotic Structural Genomics

Protein Structure Initiative

Target ID	GO.37540	
Source Organism	*Homo sapiens*	
Target Name	BC078813	
PDB Entry	2H1S	Deposition: 16-May-2006
Function	Glyoxylate reductase/ hydroxypyruvate reductase (FF/Refine: 2Q50)	
Produced From	*E. coli* B834 p(RARE2) pVP-16	
Structure by X-ray	Resolution: 2.45 Å	R-value (R-free): 20.7% (26.4%)
	No. of Residues/ASU: 1284	Monomers/ASU: 4
Data Collected At	Advanced Photon Source 23-ID-D 19-Apr-2006	
Authors	E. Bitto, G.E. Wesenberg, G.N. Phillips, Jr., C.A. Bingman	





Structural Features

Human glyoxylate reductase/hydroxypyruvate reductase (GRHPR) is a D-2-hydroxy-acid dehydrogenase that plays a critical role in the removal of the metabolic by-product glyoxylate from within the liver. Deficiency of this enzyme is the underlying cause of primary hyperoxaluria type 2 and leads to increased urinary oxalate levels, formation of kidney stones and renal failure. The crystal structure of human GRHPR contains four copies of GRHPR in the asymmetric unit. Each monomer consists of 2 $\alpha/\beta/\alpha$ globular domains. The larger, coenzyme-binding domain has a classical Rossman fold topology with the insertion of an extended dimerization loop between residues 123 and 149. The smaller domain with flavodoxin-like fold can be classified as formate/glycerate dehydrogenase substrate-binding domain. The putative active site of GRHPR lies in the cleft formed between the two domains. Several active side residues involved in ligand binding and catalysis are conserved in members of 2-hydroxy-acid dehydrogenase family. They include the catalytic triad residues His293, Glu274 and Arg269 that facilitate the hydride transfer between the substrate and NADP(H). The crystal structure of human GRHPR in complex with NADPH and reduced substrate has been solved at 2.2 Å resolution (PDB ID code 2GCG). It reveals the details of the active site organization and provides further insight into stereospecificity and likely catalytic mechanism for this enzyme (1). The preference of GRHPR for NADPH over NADH observed in kinetic assays can be explained by presence of two arginine residues in the coenzyme-binding pocket that stabilize the negative charge of the phosphate group. GRHPR has an unusual substrate specificity, preferring glyoxylate and hydroxypyruvate, but not pyruvate. Two conserved residues in the vicinity of the active site (Trp141 and Ser 296) are likely responsible for the selectivity for hydroxypyruvate.

References: (1) Booth, M.P., Conners, R., Rumsby, G., Brady, R.L. (2006) Structural basis of substrate specificity in human glyoxylate reductase/hydroxypyruvate reductase. *J Mol Biol* 360(1):178-89.

Percent Identity with Nearest PDB Structure at Time Solved	35% (1GDH)
Pfam Cluster	2-Hacid_dh
Sequence Cluster Size	3756

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